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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,927	02/07/2005	Hana Stepankova	264288US0PCT	1890

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EXAMINER	
CHO, JENNIFER Y	
ART UNIT	**PAPER NUMBER**
1621	

NOTIFICATION DATE	DELIVERY MODE
07/03/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/523,927	STEPANKOVA ET AL.	
	Examiner	Art Unit	
	JENNIFER Y. CHO	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is in response to Applicant's communication filed on 3/17/08.

Claims 1-12 are pending in this application.

The 35 U.S.C. 102 and 103(a) rejections have been withdrawn. Applicant has provided a convincing argument so that the combined references fail to teach or suggest the present invention as set forth in claim 1. However, upon further consideration, new ground(s) of rejections are made as shown herein.

Claim Rejections - 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bhattacharyya (J. Org. Chem., 1995, 60, 4928-4929), and Ciszewska et al (Journal of Labelled Compounds and Radiopharmaceuticals vol. XXXIX, No. 8 pages 651 - 668).

Applicants' claim a method of production of (-) – (S) -3-[1-(dimethylamino)ethyl]phenyl-N-ethyl-N-methylcarbamate of formula **II** or of its hydrogentartrate of formula **I**, comprising, reductive aminating methoxyacetophenone of formula **VI** to form the compound of formula **V** which is de-alkylated to the racemic amine of formula **IV** and is further resolved to the compound of formula **III**. Compound of formula **III** is reacted with compound of formula **VII,** as embodied in claim 1. Further, in the dependent claims applicants' claim the resolution of the compound of formula IV by reacting with S (+) camphor 10 sulfonic acid.

Bhattacharyya teaches the reductive amination/alkylation of the methoxyacetophenone of formula **VI** to form the compound of formula **V** (page 4929, scheme 1, table 1, entry 11).

Bhattacharyya is deficient in that it does not teach the subsequent conversion steps.

Ciszewska et al teaches O-dealkylation of compound 17, which corresponds to Applicant's compound **V**, resulting in compound 18, which corresponds to Applicant's compound **IV** and **III**. There compounds are reacted with an acid halide derivative, which corresponds with Applicant's compound **VII**, to give compound 19, corresponding to Applicant's product of compound **I**, rivastigmine hydrogentartrate (page 655, scheme).

Ciszewska et al. is deficient in that it teaches that rivastigmine hydrogentartrate contains C-14 labelled compounds, whereas the instant claims embodies unlabelled compounds. Also Ciszewska resolves the intermediate earlier in the reaction steps with an optically active acid, (see conversion of compound 15 to compound 16) rather than later in the synthetic scheme as in the instant claims. Furthermore, the dependent claims use camphor sulfonic acid as the resolving agent to resolve the compound of formula **IV** to compound of formula **III**.

In regards to the use of radiolabelled carbon and the sequence of resolving the chemical intermediate, it is the position of the Examiner that one of ordinary skill in the art, at the time of the invention, would through routine and normal experimentation determine the optimization of these limitations to provide the best effective variable depending on the results desired. Thus it would be obvious in the optimization process to use the appropriate carbon isotope and resolve the intermediate at an appropriate stage in the synthetic scheme, with the reasonable expectation that the products would have higher yields, purities and isotopic labeling. The Applicant does not show any unusual and/or unexpected results for the limitations stated.

Therefore, it would be prima facie obvious to one of ordinary skill in the art at the time of the invention, to combine the teachings of Bhattacharyya and Ciszewska et al., to achieve the predictable result of forming rivastigmine hydrogentartrate with high enantiomeric purity. The expected and desirable result would be the formation of rivastigmine hydrogentartrate with high yield and purity, which would be part of the ordinary capabilities of a person of ordinary skill in the art, in view of Bhattacharyya and

Ciszewska et al.'s teachings for the synthetic conversion of methoxyacetophenone to rivastigmine hydrogentartrate.

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bhattacharyya (J. Org. Chem., 1995, 60, 4928-4929), and Ciszewska et al (Journal of Labelled Compounds and Radiopharmaceuticals vol. XXXIX, No. 8 pages 651 - 668), in view of MacDonald et al (J Chem Soc, 1932, 2513-2519) .

Applicants' claim a method of production of (-) – (S) -3-[1-(dimethylamino)ethyl]phenyl-N-ethyl-N-methylcarbamate of formula **II** or of its hydrogentartrate of formula **I**, comprising, reductive aminating methoxyacetophenone of formula **VI** to form the compound of formula **V** which is de-alkylated to the racemic amine of formula **IV** and is further resolved to the compound of formula **III**. Compound of formula **III** is reacted with compound of formula **VII,** as embodied in claim 1. Further, in the dependent claims applicants' claim the resolution of the compound of formula IV by reacting with S (+) camphor 10 sulfonic acid.

Bhattacharyya teaches the reductive amination/alkylation of the methoxyacetophenone of formula **VI** to form the compound of formula **V** (page 4929, scheme 1, table 1, entry 11).

Bhattacharyya is deficient in that it does not teach the subsequent conversion steps.

Ciszewska et al teaches O-dealkylation of compound 17, which corresponds to Applicant's compound **V**, resulting in compound 18, which corresponds to Applicant's compound **IV** and **III**. There compounds are reacted with an acid halide derivative,

which corresponds with Applicant's compound **VII**, to give compound 19, corresponding to Applicant's product of compound **I**, rivastigmine hydrogentartrate (page 655, scheme).

Ciszewska et al. is deficient in that it teaches that rivastigmine hydrogentartrate contains C-14 labelled compounds, whereas the instant claims embodies unlabelled compounds. Also Ciszewska resolves the intermediate earlier in the reaction steps with an optically active acid, (see conversion of compound 15 to compound 16) rather than later in the synthetic scheme as in the instant claims. Furthermore, the dependent claims use camphor sulfonic acid as the resolving agent to resolve the compound of formula **IV** to compound of formula **III**.

MacDonald et al teaches (see page 2514, lines 17-22 and also see the whole document) the resolution of m-hydroxy phenylethylmethylamine using bromo camphor sulphonic acid.

In regards to the use of radiolabelled carbon and the sequence of resolving the chemical intermediate, it is the position of the Examiner that one of ordinary skill in the art, at the time of the invention, would through routine and normal experimentation determine the optimization of these limitations to provide the best effective variable depending on the results desired. Thus it would be obvious in the optimization process to use the appropriate carbon isotope and resolve the intermediate at an appropriate stage in the synthetic scheme, with the reasonable expectation that the products would have higher yields, purities and isotopic labeling. The Applicant does not show any unusual and/or unexpected results for the limitations stated.

Therefore, it would be prima facie obvious to one of ordinary skill in the art at the time of the invention, to use MacDonald et al.'s acid resolution compound for the combined teachings of Bhattacharyya and Ciszewska et al., to achieve the predictable result of forming rivastigmine hydrogentartrate with high enantiomeric purity. Furthermore, the limitations in some of the dependent claims, not expressly taught in the art, are also deemed to be obvious. One of ordinary skill in the art would be motivated to make fine adjustments and optimize these parameters to arrive at the instantly claimed invention. The expected and desirable result would be the formation of rivastigmine hydrogentartrate with high yield and purity, which would be part of the ordinary capabilities of a person of ordinary skill in the art, in view of Bhattacharyya and Ciszewska et al.'s teachings for the synthetic conversion of methoxyacetophenone to rivastigmine hydrogentartrate.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Y. Cho whose telephone number is (571) 272 6246. The examiner can normally be reached on 9 AM - 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571) 272 0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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